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Peters, M.J.; Vis, M.; van Halm, V.P.; Wolbink, G.J.; Voskuijl, A.E.; Lems, W.F.; Dijkmans, B.A.C.; Twisk, J.W.R.; de Koning, M.H..; van de Stadt, R.J.; Nurmohamed, M.T.

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EXTENDED REPORT

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M J L Peters, M Vis, V P van Halm, G J Wolbink, A E Voskuyl, W F Lems, B A C Dijkmans, J W R Twisk, M H M T de Koning, R J van de Stadt, M T Nurmohamed

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See end of article for authors' affiliations

Correspondence to: Dr M T Nurmohamed, Departments of Internal Medicine and Rheumatology, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands; mt.nurmohamed@vumc.nl

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Objective: To evaluate the effects of infliximab and corticosteroid treatment on the lipid profile in patients with active rheumatoid arthritis (RA).

Methods: Infliximab infusions were given at weeks 0, 2, 6 and then every 8 weeks. Before each infusion, disease activity parameters (Disease Activity Index 28-Joint Score (DAS28)) C reactive protein (CRP) and lipid levels (total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, apolipoprotein A1 (apo A1) and apolipoprotein B) were measured in 80 consecutive patients with RA, who completed the study period of 48 weeks. Longitudinal analyses were used to investigate (1) the course of lipid levels over a period of time and (2) the relationship between lipids, prednisone dose and disease activity.

Results: Infliximab treatment causes a significant reduction in disease activity and a concomitant decrease in prednisone dose. Although they initially improved significantly, all lipid levels had returned to baseline levels after 48 weeks, except for apo A1. Longitudinal analyses revealed significant yet opposite associations between lipid levels and disease activity and between lipid levels and prednisone dose. DAS28 improvement by 1 point was associated with an increase of 0.016 mmol/l (0.618 mg/dl) total cholesterol and 0.045 mmol/l (1.737 mg/dl) HDL-cholesterol. Reduction of 10 mg prednisone was associated with a decrease of 0.04 mmol/l (1.544 mg/dl) total cholesterol and 0.16 mmol/l (6.177 mg/dl) HDL-cholesterol.

Conclusion: Overall, no changes in serum lipid levels were observed after 48 weeks of infliximab treatment. The initial beneficial effects of infliximab on the lipid profile, by means of a reduction of disease activity, are attenuated by a concomitant decrease in prednisone dose.

Rheumatoid arthritis (RA) is a chronic, inflammatory disorder of the joints. Patients with RA have an increased morbidity and mortality compared with the general population. Mortality from cardiovascular disease (CVD) is the leading cause of death observed in patients with RA.[1] This excess cardiovascular mortality in patients with RA is predominantly due to accelerated atherosclerosis.[2]

A well-known cause of atherosclerosis is an atherogenic lipid profile. In particular, low levels of high-density lipoprotein (HDL)-cholesterol, and high levels of total cholesterol, low-density lipoprotein-cholesterol and triglycerides are associated with an increased prevalence of CVD in the general population.[3] An important prognostic indicator for future CVD is the atherogenic index,which is the ratio between total cholesterol and HDL-cholesterol.[4] New data indicate that apolipoproteins, which are protein parts of the lipoprotein complex, are possibly better predictors for CVD. High levels of apolipoprotein B (apo B) and an increased apolipoprotein B:apolipoprotein A1 ratio (apo B:apo A1) are associated with an increased cardiovascular risk, whereas higher levels of apo A1 are protective for developing CVD.[5 6]

Several studies reported that RA is associated with an unfavourable lipid profile, particularly in patients with active disease.[7–9] These studies show that active RA is associated with lower levels of HDL-cholesterol compared with healthy controls, leading to a higher—that is, unfavourable—atherogenic index. Hence, an atherogenic lipid profile may be part of the cause of the increased cardiovascular risk in patients with RA.

Growing evidence suggests that inflammation in RA is associated with a worsening of the lipid profile,[10 11] which improves on effective antirheumatic treatment.[12 13] We previously reported that normalisation of the lipid profile in patients with RA occurred more rapidly in combination treatment with methotrexate (MTX), sulphasalazine and prednisone than in treatment with sulphasalazine alone, thereby demonstrating the temporal relationship between decreasing disease activity and improvement of the atherogenic index.[14] However, because of the limited duration of the study, we were unable to answer the question of whether this difference was due to improved disease suppression or changes in prednisone dose.

In another study, we found that treatment with anti-tumour necrosis factor therapy leads to a significant increase of both total cholesterol and HDL cholesterol levels, which was inversely related with disease activity. The atherogenic index, however, remained constant during the 6-week study period.[15]

Thus far, data regarding lipid changes during immunosuppressive treatment are contradictory,[16 17] and studies observing lipid changes during long-term immunosuppressive treatment are lacking. In the present study, longitudinal analyses were performed to investigate (1) the longitudinal course of lipid levels, including apolipoproteins, over time during immunosuppressive treatment—that is, infliximab—and (2) the longitudinal relationship between lipids and indicators of disease activity and between lipids and prednisone doses.

PATIENTS AND METHODS

Consecutive patients with active RA (defined as a Disease Activity Index 28-Joint Score (DAS28) of at least 3.2) who were referred to the Slotervaart Hospital, Amsterdam, The Netherlands, for treatment with infliximab were included. All patients with RA fulfilled the American College of

Abbreviations: apo A1, apolipoprotein A1; apo B, apolipoprotein B; CVD, cardiovascular disease; DAS28, Disease Activity Index 28-Joint Score; GEEs, general estimation equations; HDL, high-density lipoprotein; RA, rheumatoid arthritis; MTX, methotrexate

Rheumatology criteria.[18] Infusions with infliximab were given at weeks 0, 2, 6 and 14 weeks, and from thereon every 8 weeks. Generally, infliximab was given in combination with stable doses of MTX. Infliximab was administered intravenously at a starting dose of 3 mg/kg. In patients with inadequate response, as judged by the patients' rheumatologist, the dose of infliximab could be increased to 7.5 mg/kg. Blood samples (non-fasting) were collected in the morning, before each infusion at weeks 0, 6, 22 and 48 and were stored at −70℃ until analyses. Total cholesterol, HDL-cholesterol, triglycerides, apo A1 and apo B concentrations were measured and the total cholesterol/HDL cholesterol and apo B:apo A1 ratios were calculated. At each visit disease activity, defined as DAS28,[19] and drug treatment were assessed. In all, 108 patients were included in the cohort, but 28 patients dropped out in the first year of treatment: 22 (78.5%) because of non-response, 5 (18%) because of side effects and 1 (3.5%) patient who died owing to unrelated events. Thus, the data from 80 patients were eligible for analyses. The baseline characteristics of the dropout patients were comparable to those of the patients included in the study (data not shown). Thus, all included patients completed the study period of 48 weeks and the patients who dropped out (n = 28) were not included for the analysis. There were no (additional) exclusion criteria.

Lipids

Total serum cholesterol (<5.0 mmol/l (193 mg/dl)) and triglycerides (<2.2 mmol/l, 196 mg/dl)) were measured by an enzymatic method using Roche clinical chemistry analysers. HDL-cholesterol (men, >0.9 mmol/l (35 mg/dl)); women, >1.1 mmol/l (42 mg/dl)) was determined enzymatically with polyethylene glycol-modified enzymes. The atherogenic index was calculated using the following formula: atherogenic index = total/HDL-cholesterol. Apo A1 (men, 1.04–2.02 g/l; women, 1.08–2.25 g/l) and apo B (men, 0.66–1.33 g/l; women, 0.60–1.17 g/l) were analysed by an immunoturbidimetric method, using assays supplied by Roche Diagnostics (Basel, Switzerland).

As it was expected that only small differences in the concentration of analyses could be significant, collected sera were first stored frozen and subsequently analysed on the same day in a single run, with all sera belonging to one person grouped together. This set-up produces within-group analytical coefficients of variation for the analyses in their reference range of <1%.

Statistical analyses

As some patients were treated with prednisone, differences in lipid profiles between prednisone users (yes/no) were analysed by using independent t tests for normally distributed variables (ie, HDL-cholesterol, apo A1, apo B and the apo B:apo A1 ratio), and Mann–Whitney U tests for not normally distributed variables (ie, total cholesterol, atherogenic index and triglycerides).

The time course of lipid levels during treatment with infliximab was investigated by using general estimation equations (GEEs). This regression technique was used as it adjusts for dependency of several measurements within one subject and is capable of dealing with unequally spaced time intervals and with missing data.[20] For this analysis, each lipid value was included separately as a dependent variable and time was included as a categorical independent variable.

GEE analyses were also used to investigate the influence of indicators of disease activity (ie, DAS28 score and C reactive protein (CRP)) and prednisone dose on all lipid levels. Hence, we performed two analyses: (1) GEE analyses including a lipid value and an indicator of disease activity or prednisone dose: for example, total cholesterol as a dependent variable and DAS28 as an independent variable, total cholesterol as a dependent variable and CRP as an independent variable, and total cholesterol as a dependent variable and prednisone as an independent variable. (2) GEE analyses including a lipid value and an indicator of disease activity corrected for prednisone dose. With GEE analyses, the development of a certain lipid is associated with the development of disease activity or prednisone dose, resulting in one regression coefficient. All analyses were adjusted for age and gender. As the distributions of total cholesterol, atherogenic index and triglycerides were not normal, a log transformation was performed before the GEE analyses. All analyses were performed with STATA V.7 and p values <0.05 were considered significant.[21]

RESULTS

Patients

The study population consisted of 80 (62 women and 18 men) consecutively included patients with RA with a mean (SD) age of 56 (14) years. The median disease duration was 10 (range 0–59) years; 55 (69%) patients were IgM-rheumatoid factor positive and 67 (82%) patients had erosions. At baseline, statins were used by 4 (5%) patients and diabetes mellitus was reported by 2 (2%) patients. During the study period, none of the included patients started statins or glucose-lowering treatment. In all, 77 (96%) patients used concomitant MTX at a stable dose—that is, 15 mg/week at all time points—and 35 (44%) patients used prednisone at the start of the study (mean prednisone dose 8.3 mg/day). As expected, treatment with infliximab leads to a significantly better DAS28-score at 48 weeks compared with baseline: 5.7 vs 3.9 (p<0.01).

Lipids

Table 1 shows the course of lipid levels over time during treatment with infliximab. Patients who used prednisone had higher total cholesterol and HDL-cholesterol levels and a lower atherogenic index at baseline, but these differences did not reach statistical significance.

After 6 weeks of treatment with infliximab, total cholesterol levels increased by 6.1% (p<0.01) and HDL-cholesterol levels increased by 10.3% (p<0.01), resulting in a 6.4% decrease of the atherogenic index (p<0.01). In the next period (6–22 weeks) both total cholesterol and HDL-cholesterol levels decreased, but remained significantly increased compared with baseline. At 48 weeks, total cholesterol and HDL-cholesterol levels approached baseline levels. As total cholesterol and HDL-cholesterol levels moved towards baseline levels, the atherogenic index revealed no significant difference compared with the baseline index at 22 and 48 weeks. Triglycerides levels did not change during the whole treatment period.

Compared with baseline, apo A1 levels increased by 4.5% at 48 weeks (p<0.01), whereas apo B levels and the apo B:apo A1 ratio did not change significantly at 48 weeks compared with baseline.

Lipids and disease activity

The course of lipids over time was compared with the course of disease activity after adjustment for age and gender (table 2). GEE analyses yielded a significant inverse association between disease activity and lipid levels. Changes in disease activity (DAS28) were significantly related with changes in HDL-cholesterol and total cholesterol levels. This means that if disease activity according to DAS28 decreases by 1 point, total cholesterol will raise 0.016 mmol/l (0.618 mg/dl) and HDL-cholesterol will increase by 0.045 mmol/l (1.737 mg/dl), resulting in a more favourable, that is, lower, atherogenic index. Similarly, the individual inflammation parameter CRP was significantly inversely associated with both HDL-cholesterol and total cholesterol levels. Moreover, the analyses showed that disease activity was inversely

Table 1 Total cholesterol, high-density lipoprotein- cholesterol, triglycerides (mmol/l), apolipoprotein A1 (apo A1), apolipoprotein B (apo B; g/l) and the atherogenic index and apo B/apo A-1 ratio during treatment with infliximab

Variable	Baseline	6 weeks	22 weeks	48 weeks
Median (range) total cholesterol (mmol/l)	4.79 (2.70–8.10)	5.08 (2.79–9.18)*	4.94 (2.90–10.42)*	4.81 (3.21–7.29)
Mean (SD) HDL-cholesterol (mmol/l)	1.46 (0.50)	1.61 (0.54)*	1.55 (0.53)*	1.53 (0.51)
Median (range) atherogenic index	3.42 (1.74–7.78)	3.20 (1.59–8.63)*	3.43 (1.67–8.08)	3.38 (1.62–10.70)
Median (range) triglycerides (mmol/l)	1.26 (0.62–4.40)	1.39 (0.52–3.80)*	1.32 (0.46–3.36)	1.26 (0.62–3.48)
Mean (SD) apo A1 (g/l)	1.58 (0.35)	1.70 (0.33)*	1.65 (0.33)*	1.65 (0.33)*
Mean (SD) apo B (g/l)	0.93 (0.23)	0.95 (0.24)	0.94 (0.24)	0.93 (0.19)
Mean (SD) apo B:Apo A1 ratio	0.62 (0.20)	0.58 (0.20)*	0.59 (0.18)	0.59 (0.16)

apo B:apo A1, apolipoprotein B:apolipoprotein A1 ratio; HDL, high-density lipoprotein.
*$p<0.05$ Compared with baseline (performed by general estimation equation analyses).

related with apo A1, resulting in a lower, that is, more favourable, apo B:apoA1 ratio.

Lipids and prednisone

During treatment with infliximab, lipid levels were compared with changes in prednisone dose at different time points after adjustment for age and gender (table 2). Changes in prednisone dose were related to changes in HDL-cholesterol and total cholesterol. Prednisone changes, however, had a greater influence on HDL-cholesterol than on total cholesterol levels, resulting in an inverse association between prednisone dose and the atherogenic index. In other words, a higher prednisone dose is associated with a lower, that is, more favourable atherogenic index. Furthermore, the prednisone dose seemed to have a significant positive relationship with apo A1, leading to a significant inverse association with the apo B:apo A1 ratio.

The reported associations between lipids and disease activity and between lipids and prednisone did not change when both prednisone and disease activity parameters were included as independent variables in the same regression analysis (data not shown).

Because of the favourable effect of infliximab on the DAS28 score, the prednisone dose was gradually decreased from a median dose of 8.3 to 4.6 mg/day. Subgroup analysis revealed no significant differences with regard to cholesterol levels between patients with RA with prednisone and without prednisone at all time points.

DISCUSSION

In this study, we observed a significant increase of total cholesterol and HDL-cholesterol levels after 6 weeks of infliximab treatment, which gradually returned to baseline after 48 weeks. As a result, improvement of the atherogenic index at 6 weeks was not observed from 22 weeks onwards. Longitudinal data analyses—that is, GEE analyses—revealed that lowering the prednisone dose attenuated the effects of infliximab on total cholesterol and HDL-cholesterol levels and its main protein part apo A1, thereby abolishing the improvement of the atherogenic index and the apo B:apo A1 ratio. Nevertheless, apo A1 levels remained significantly increased after 48 weeks of treatment, which might be important as accumulating epidemiological evidence indicates that high levels of apo A1 are strongly related with a lower risk for future CVD.[5 6]

Recent research has shown that systemic inflammation plays a pivotal role in the development of atherosclerosis. Immune cells dominate early atherosclerotic lesions, their effector molecules accelerate progression of the lesions and inflammation elicits CVD.[22] Hence, inflammation might be the key to explaining the enhanced cardiovascular risk in patients with RA.[23] Moreover, inflammation induces the acute-phase response leading to lipid changes and alterations in lipoprotein metabolism. Most of these changes—that is, decreased levels of HDL-cholesterol and apo A1—are pro-atherogenic and ultimately may contribute to the increased cardiovascular risk in RA. In this study, a decreasing disease activity resulted in a lower, atherogenic index as a result of higher total cholesterol levels and even more pronounced higher HDL levels. In addition, a decrease of disease activity led to a better apo B:apo A1 ratio, because of significantly increased apo A1 levels. These findings are in line with other studies reporting an inverse association between inflammatory markers (erythrocyte sedimentation rate and CRP) and HDL-cholesterol or its apo A1.[12 13]

Differences reported in this study are small and may therefore question their clinical relevance. Several studies, however, highlight the importance of lipid changes even though the observed differences are small. The Lipid Research Clinics Coronary Primary Prevention Trial and the Framingham Study, for example, show that a 0.026 mmol/l (1 mg/dl) increment of baseline HDL-cholesterol is associated with an approximately 3.5% risk reduction for coronary heart disease.[24 25] Another study performed by Rubins *et al*[26] revealed that a 6% increase in HDL-cholesterol is associated with an absolute risk reduction of 4.4% of death from coronary heart disease or non-fatal infarction. Although these findings cannot be directly extrapolated to our study, they show the clinical importance of only small lipid changes. Moreover, several recent observations indicate that apo-B and apo A1 may in fact

Table 2 Relationship between lipid items, indicators of disease activity and prednisone

Variable	Atherogenic index Coefficient (SE)	Total cholesterol (mmol/l) Coefficient (SE)	HDL-cholesterol (mmol/l) Coefficient (SE)	Apo B:Apo A1 Coefficient (SE)	Apo B (g/l) Coefficient (SE)	Apo A1 (g/l) Coefficient (SE)
Indicators of disease activity						
1-point decrease/difference of DAS28	–0.016 (0.008)*	0.016 (0.005)*	0.045 (0.013)*	–0.013 (0.005)*	0.004 (0.004)	0.036 (0.009)*
10-points decrease/difference of CRP	–0.026 (0.001)*	0.024 (0.001)*	0.067 (0.001)*	–0.014 (0.001)*	0.009 (0.001)	0.045 (0.001)*
Reduction/difference of 1 mg prednisone	0.009 (0.004)*	–0.004 (0.002)*	–0.016 (0.006)*	0.005 (0.002)*	0.001 (0.002)	–0.009 (0.004)*

CRP, C reactive protein; DAS28, Disease Activity Index 28-Joint Score; HDL, high-density lipoprotein.
Values are given as regression coefficients (SE), and standard errors estimated by general estimation equation analyses for each lipid item as a continuous outcome variable. All analyses were adjusted for age and gender.
*$p<0.05$.

be more powerful predictors of risk for CVD than the conventional lipid values.[5 6 22 27] This is important and might be clinically relevant, as this study indicates that apo A1 remains significantly increased during the whole treatment period.

Mechanisms underlying the decrease of HDL-cholesterol during inflammation are not firmly established. Our findings, however, suggest that alterations in prednisone dose are relevant. We showed that lowering the prednisone dose results in a decrease of total cholesterol levels that is predominantly due to a decrease in HDL-cholesterol leading to a higher atherogenic index (as the effect on total cholesterol was less pronounced). By contrast, increasing the prednisone dose might have favourable effects on the lipid profile. Nevertheless, it is highly uncertain whether or not this postulated beneficial effect is ultimately offset by other cardiovascular side effects of long-term prednisone use, such as insulin resistance and hypertension.

In addition to a previous study performed by our study group,[14] the present study reveals additional insights into the influence of prednisone and disease activity on the lipid profile as both have a significant, but opposing, and more pronounced influence on HDL-cholesterol than on total cholesterol.

MTX may provide a substantial survival benefit, largely by reducing mortality from CVD.[28] Patients in our investigation were taking stable MTX doses during the treatment period. Hence, we were not able to evaluate the effect of MTX on the lipid profile. Our results, however, do indicate that suppression of inflammation leads to a more favourable lipid profile, which may also be conceivable for MTX.

There might be additional explanations for the observed longitudinal lipid changes. First, exercise increases HDL-cholesterol in healthy individuals,[29] and immunosuppressive treatment is associated with a substantial clinical improvement whereby patients with RA will increase their physical activity. Second, patients with RA with a high disease activity have higher levels of tumour necrosis factor (TNF), which is associated with rheumatoid cachexia.[30] Treatment with infliximab obviously leads to lower levels of the TNF, therefore possibly leading to a better dietary intake resulting in increased lipid levels. Finally, we have to consider the possibility that the observed lipid changes are a direct effect of biologicals through blocking TNFα.

In conclusion, the present investigation shows that immunosuppressive treatment with infliximab might have beneficial effects on the increased cardiovascular risk in patients with RA via several mechanisms: (1) because of its anti-inflammatory effects; (2) indirectly as a cause of lower prednisone doses; and (3) through a small, anti-atherogenic effect on the lipid profile. Prospective cardiovascular outcome studies are needed to establish whether or not immuno-suppressive treatment indeed results in a lower cardiovascular risk.

Authors' affiliations

M J L Peters, M Vis, V P van Halm, A E Voskuyl, W F Lems, B A C Dijkmans, Department of Rheumatology, VU University Medical Center, Amsterdam, The Netherlands
V P van Halm, G J Wolbink, W F Lems, B A C Dijkmans, M H M T de Koning, R J van de Stadt, M T Nurmohamed, Department of Rheumatology, Jan van Breemen Institute, Amsterdam, The Netherlands
G J Wolbink, CLB Sanquin, Amsterdam, The Netherlands
W F Lems, B A C Dijkmans, Department of Rheumatology, Slotervaart Hospital, Amsterdam, The Netherlands
J W R Twisk, Department of Clinical Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands
M T Nurmohamed, Department of Internal Medicine, VU University Medical Center, Amsterdam, The Netherlands

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